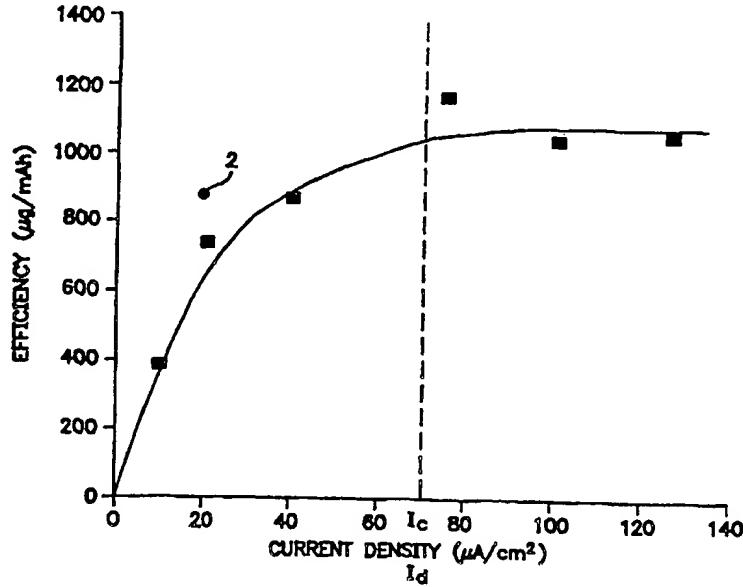




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(54) Title: ELECTROTRANSPORT AGENT DELIVERY METHOD AND APPARATUS



(57) Abstract

An electrotransport agent delivery device (10) for delivering a therapeutic agent through intact skin, and a method of operating same, is provided. The device applies a pulsing electrotransport current wherein the length of the applied current pulses is at least 5 msec and preferably at least 10 msec. Most preferably, the current pulses have a magnitude above a critical level (I_c) at which the skin is transformed into a higher electrotransport delivery efficiency (E) state.

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1 ELECTROTRANSPORT AGENT DELIVERY METHOD AND APPARATUS

2

3

4

TECHNICAL FIELD

5

6 The present invention generally concerns a method and apparatus for
7 the electrically assisted delivery of a therapeutic agent (e.g., a drug) through a
8 body surface (e.g., skin) at increased efficiency. This invention is particularly
9 applicable to the electrotransport of highly potent therapeutic agents which
10 are to be delivered at small dosage levels.

11

12 BACKGROUND OF THE INVENTION

13

14 The present invention concerns in vivo methods and apparatuses
15 for electrotransport delivery of therapeutic agents, typically drugs,
16 into a patient. Herein the terms "electrotransport", "iontophoresis" and
17 "iontophoretic" are used to refer to methods and apparatus for transdermal
18 delivery of therapeutic agents, whether charged or uncharged, by
19 means of an applied electromotive force to an agent-containing reservoir.
20 The particular therapeutic agent to be delivered may be completely charged
21 (i.e., 100% ionized), completely uncharged, or partly charged and partly
22 neutral. The therapeutic agent or species may be delivered by
23 electromigration, electroosmosis or a combination of these processes.
24 Electroosmosis has also been referred to as electrohydrokinesis, electro-
25 convection, and electrically-induced osmosis. In general, electroosmosis
26 of a therapeutic species into a tissue results from the migration of solvent,
27 in which the species is contained, as a result of the application of
28 electromotive force to a reservoir containing the therapeutic species.
29 As used herein, the terms "electrotransport", "iontophoresis" and
30 "iontophoretic" refer to (1) the delivery of charged drugs or agents by
31 electromigration, (2) the delivery of uncharged drugs or agents by the

1 process of electroosmosis, (3) the delivery of species by transport
2 processes which include an electroporation step (See, e.g., Weaver et al
3 US Patent 5,019,034), (4) the delivery of charged drugs or agents by the
4 combined processes of electromigration and electroosmosis, and/or (5)
5 the delivery of a mixture of charged and uncharged drugs or agents by the
6 combined processes of electromigration and electroosmosis, combinations
7 of the above processes to deliver either or both of charged or uncharged
8 species.

9 Iontophoretic devices for delivering ionized drugs through the
10 skin have been known since the early 1900's. See for example Deutsch
11 US Patent 410,009. In presently known electrotransport devices, at least
12 two electrodes or electrode assemblies are used. Both electrodes/electrode
13 assemblies are disposed so as to be in intimate electrical contact with some
14 portion of the skin of the body. One electrode, called the active or donor
15 electrode, is the electrode from which the ionic substance, agent,
16 medicament, drug precursor or drug is delivered into the body through
17 the skin by iontophoresis. The other electrode, called the counter or
18 return electrode, serves to close the electrical circuit through the body.
19 In conjunction with the patient's skin contacted by the electrodes, the circuit
20 is completed by connection of the electrodes to a source of electrical energy,
21 e.g., a battery. For example, if the ionic substance to be delivered into the
22 body is positively charged, then the positive electrode (the anode) will be the
23 active electrode and the negative electrode (the cathode) will serve to
24 complete the circuit. If the ionic substance to be delivered is negatively
25 charged, then the cathodic electrode will be the active electrode and the
26 anodic electrode will be the counter electrode.

27 As is discussed above, electrotransport delivery devices can be used
28 to deliver uncharged drugs or agents into the body, e.g., transdermally. This
29 is accomplished by a process called electroosmosis. Electroosmosis is the
30 (e.g., transdermal) flux of a liquid solvent (e.g., the liquid solvent containing

- 1 the uncharged drug or agent) which is induced by the presence of an electric
- 2 field imposed across the skin by the donor electrode.

3 Electrotransport electrode assemblies/devices generally include a
4 reservoir or source of the beneficial agent or drug (preferably an ionized or
5 ionizable species or a precursor of such species), which is to be delivered into
6 the body by electrotransport. Examples of such reservoirs or sources include
7 a pouch as described in Jacobsen US Patent 4,250,878, a pre-formed gel
8 body as disclosed in Webster US Patent 4,383,529 and Ariura, et al
9 US Patent 4,474,570 and a receptacle containing a liquid solution as
10 disclosed in Sanderson, et al US Patent 4,722,726. Such drug reservoirs
11 are connected to the anode or the cathode of an electrotransport device to
12 provide a fixed or renewable source of one or more desired species or
13 agents. Electrical current is typically applied to the reservoir by means of a
14 current distributing member, which may take the form of a metal plate, a foil
15 layer, a conductive screen, or a polymer film loaded with an electrically
16 conductive filler such as silver or carbon particles. The current distributing
17 member, including any appropriate connectors and associated connective
18 conductors such as leads, and the reservoir comprise an electrode assembly
19 herein.

20 The prior art has recognized that "competitive" ionic species having the
21 same charge (i.e., the same sign) as the drug ions being delivered by
22 electrotransport have a negative impact on electrotransport drug delivery
23 efficiency. The efficiency (E) of electrotransport delivery of a particular
24 species is defined herein as the rate of electrotransport delivery of that
25 species per unit of applied electrotransport current (mg/mA-h). The prior art
26 further recognized that competitive ionic species were inherently produced
27 during operation of these devices. The competitive species produced are
28 dependent upon the type of electrode material which is in contact with the
29 drug solution. For example, if the electrode is composed of an
30 electrochemically inert material (e.g., platinum or stainless steel), the

1 electrochemical charge transfer reaction occurring at the electrode surface
2 tended to be water electrolysis since water is the overwhelmingly preferred
3 liquid solvent used in electrotransport drug solutions. Water electrolysis
4 produces competing hydronium ions at the anode (in the case of cationic
5 electrotransport drug delivery) and competing hydroxyl ions at the cathode
6 (in the case of anionic electrotransport drug delivery). On the other hand,
7 if the electrode is composed of an electrochemically oxidizable or reducible
8 species, then the electrode itself is oxidized or reduced to form a competitive
9 ionic species. For example, Untereker et al US Patent 5,135,477 and
10 Petelenz et al US Patent 4,752,285 recognize that competitive ionic species
11 are electrochemically generated at both the anode and cathode of an
12 electrotransport delivery device. In the case of an electrotransport delivery
13 device having a silver anodic donor electrode, application of current through
14 the silver anode causes the silver to become oxidized ($\text{Ag} \rightarrow \text{Ag}^+ + \text{e}^-$)
15 thereby forming silver cations which compete with the cationic drug for
16 delivery into the skin by electrotransport. The Untereker and Petelenz
17 patents teach that providing a cationic drug in the form of a halide salt causes
18 a chemical reaction which removes the "competing" silver ions from the donor
19 solution (i.e., by reacting the silver ions with the halide counter ion of the drug
20 to form a water insoluble silver halide precipitate; $\text{Ag}^+ + \text{X}^- \rightarrow \text{AgX}$), thereby
21 achieving higher drug delivery efficiency. In addition to these patents,
22 Phipps et al PCT/US95/04497 filed on April 7, 1995 teaches the use of
23 supplementary chloride ion sources in the form of high molecular weight
24 chloride resins in the donor reservoir of a transdermal electrotransport
25 delivery device. These resins are highly effective at providing sufficient
26 chloride for preventing silver ion migration, yet because of the high molecular
27 weight of the resin cation, the resin cation is effectively immobile and hence
28 cannot compete with the drug cation for delivery into the body.

1 The prior art has long recognized that the application of electric
2 current through skin causes the electrical resistance of the skin to decrease.
3 See, for example, Haak et al US Patent 5,374,242 (Figure 3). Thus, as the
4 electrical resistance of the skin drops, lower voltages are needed to drive a
5 particular level of electrotransport current through the skin. This same
6 phenomenon is observed in a technique referred to as "electroporation"
7 of the skin. See Weaver et al US Patent 5,019,034. Electroporation
8 involves the application of short, high voltage electrical pulses to produce
9 what is characterized as a transient (e.g., decreasing to normal levels in
10 10 to 120 sec. for excised frog skin) increase in tissue permeability.
11 Electroporation is also characterized by the creation of pores in lipid
12 membranes due to reversible electrical breakdown. Electroporation does not,
13 itself, deliver any drug but merely prepares the tissue thereby treated for
14 delivery of drug by any of a number of techniques, one of which is
15 iontophoresis.

16

17 DISCLOSURE OF THE INVENTION

18

19 The present invention arises from the discovery that when delivering a
20 therapeutic agent (eg, a drug) via electrotransport through a living body
21 surface (eg, skin) of an animal (eg, a human) using a pulsing electrotransport
22 current, the efficiency of electrotransport agent delivery is increased by
23 maintaining the width of the applied current pulses above a minimum period
24 of time. For certain drugs delivered transdermally to humans via
25 electrotransport, this minimum period has been found to be about 5 msec,
26 and preferably about 10 msec. In general, this discovery means that lower
27 frequency pulsing electrotransport currents tend to provide more efficient
28 agent delivery than higher frequency pulsing electrotransport currents, since
29 the longer the pulse width, the fewer the number of pulses which can be
30 applied in any unit of time. Thus, when using pulsing currents having pulse

1 widths of at least about 5 msec, and preferably at least about 10 msec, the
2 pulsing frequencies tend to be less than about 100 Hz and more preferably
3 less than about 10 Hz.

4 As used herein, the term "electrotransport agent delivery efficiency (E)"
5 means the rate of transdermal electrotransport delivery (mg/h) per unit of
6 applied electrotransport current (mA) and expressed in units of micrograms of
7 agent (i.e., drug) delivered per milliamp-hour of applied electric current
8 ($\mu\text{g}/\text{mA}\text{h}$). Electrotransport delivery efficiency, in some aspects of its
9 meaning, is analogous to transport number. Transport number is a unitless
10 quantity, less than one, indicating the fractional charge carried by a particular
11 ionic species, e.g., a drug or agent, during electrotransport delivery.
12 Electrotransport delivery efficiency, as defined herein, is more broadly
13 applicable to include the transport of uncharged species and is more
14 reflective of the scope of the invention.

15 The terms "pulsing current" and "pulsed current" as used herein refer
16 to an applied electrotransport current having a periodic (i.e., the waveform
17 repeats over time and has a wave length and a frequency) waveform shape
18 comprised of a first segment of applied electrotransport current having a first
19 average current magnitude, and a second segment of applied electrotransport
20 current having a second average current magnitude, the second average
21 current magnitude being less than the first average current magnitude. In
22 general, the second average current magnitude is less than about 70% of the
23 first average current magnitude, more typically less than about 50% of the
24 first average current magnitude and most typically less than about 25% of the
25 first average current magnitude. The second average current magnitude can
26 be zero or substantially zero, but in any event is substantially less than the
27 first average current magnitude.

28 The present invention is not limited to any particular periodic pulsed
29 waveform shape and may take the form of any of various types of periodic
30 waveforms including sinusoidal, trapezoidal, square or rectangular current

1 waveforms. A square pulsed current waveform shape is particularly suitable
2 for practicing this invention.

3 In a preferred embodiment of the present invention, the first average
4 current magnitude is sufficient to produce a current density which is equal to
5 or greater than a critical current density, I_c . Applied electrotransport current
6 densities (generally expressed in units of microamperes per square
7 centimeter ($\mu\text{A}/\text{cm}^2$) herein) above this critical level result in even further
8 enhancement of electrotransport transdermal agent delivery efficiency. This
9 "further" enhancement of the skin's electrotransport delivery efficiency has
10 been found to be non-transitory, i.e., to last for at least several minutes to
11 several hours or longer after application of current densities and over periods
12 of time in accordance with this preferred embodiment of the invention. This
13 preferred embodiment of the invention induces (e.g., through a pre-treatment
14 or pre-application step in which species are delivered) a high efficiency drug-
15 transmissive state in the skin to which an electrotransport drug delivery
16 device is applied. The induced, high efficiency state continues and can be
17 utilized to deliver drug or other therapeutic agent transdermally with increased
18 efficiency. In usual circumstances, this will permit delivery of drug with more
19 precise control and at a lower current. This phenomenon has only been found
20 in the transdermal delivery of drug or agent through intact living skin or tissue
21 (i.e., *in vivo*) and is not exhibited in dead skin (i.e., excised skin through which
22 species are electrotransported *in vitro*). In this manner, the treated skin
23 exhibits a statistically significant, non-transitory increase in drug delivery
24 efficiency relative to skin which has not been so treated. Generally speaking,
25 utilization of this preferred embodiment of the invention significantly increases
26 the drug/agent delivery efficiency and reduces or eliminates variability in the
27 drug delivery efficiency of the skin site which is so treated. Since
28 electrotransport delivery efficiency remains elevated and less variable after
29 utilization of this embodiment (relative to untreated skin), utilization of this

1 embodiment of the invention permits the delivery of drug or agent through
2 intact skin by electrotransport with increased control and efficiency.

3 Thus, in one aspect, the present invention is a method of
4 electrotransport drug or agent delivery through a body surface involving the
5 steps of delivering a therapeutic agent by a pulsing electrotransport current,
6 the current pulses being sufficiently long (i.e., at least about 5 msec and
7 preferably at least about 10 msec), to reduce or avoid capacitive loss and
8 thereby deliver the agent at an enhanced electrotransport delivery efficiency
9 (E). In a preferred aspect, the current pulses have a sufficient magnitude to
10 produce a current density greater than or equal to I_c , to convert the
11 electotransport delivery efficiency of the body surface (i.e., the skin) through
12 which the agent is delivered to a non-transitory state of higher
13 electrotransport delivery efficiency. Thereafter, the drug or agent is delivered
14 through the body surface while the body surface is in the higher efficiency
15 transfer state.

16

17 BRIEF DESCRIPTION OF THE DRAWINGS

18

19 A better understanding of the present invention, as well as other
20 objects and advantages thereof, will become apparent upon consideration of
21 the following modes for carrying out the invention especially when taken with
22 the accompanying drawings, wherein:

23

24 FIG. 1 is a graph of transdermal electrotransport drug delivery
25 efficiency (E) versus applied electrotransport current density (I_d) for in vivo
26 electrotransport transdermal delivery of fentanyl;

27 FIG. 2 is a graph of electrotransport current versus time, showing three
28 pulsed current waveforms having the same pulsing frequency but differing
29 pulse widths and duty cycles;

1 FIG. 3 is an exploded perspective view of a transdermal
2 electrotransport drug delivery device which can be used in accordance with
3 the method of the present invention;

4 FIG. 4 is a graph of electrotransport current versus time, showing two
5 pulsed waveforms having the same peak current and pulse width but different
6 pulsing frequencies;

7 FIG. 5 is a graph of mean serum fentanyl concentration versus time,
8 showing how initial electrotransport administered doses increase subsequent
9 fentanyl delivery through a 24 hour period;

10 FIG. 6 is average serum fentanyl concentration, as a function of time,
11 for applied electrotransport current densities of 10, 20 and 40 $\mu\text{A}/\text{cm}^2$;

12 FIG. 7 is a graph of serum fentanyl concentration versus time for
13 delivery of fentanyl at pulsing frequencies of 1, 10 and 625 Hz; and

14 FIG. 8 is a graph of serum goserelin concentration versus time,
15 for applied electrotransport current densities of 50 and 100 $\mu\text{A}/\text{cm}^2$.

16

17 MODES FOR CARRYING OUT THE INVENTION

18

19 The present invention is based upon the discovery that when delivering
20 an agent (e.g., a drug) transdermally through intact skin via electrotransport
21 using a pulsing electrotransport current, the efficiency (E) of transdermal
22 electrotransport agent (e.g., drug) delivery is increased by maintaining the
23 width of the current pulses greater than 5 msec and preferably greater than
24 10 msec. Since pulse width is inherently related to pulsing frequency, the
25 discovery means that the efficiency of electrotransport delivery, when using a
26 pulsing current, is greater at lower pulsing frequencies. Preferably, the
27 pulsing frequency is maintained below about 100 Hz, and more preferably
28 less than about 10 Hz. By maintaining longer pulse widths (and
29 correspondingly lower pulsing frequencies), the inefficiencies associated with
30 "charging up" the electrical capacitance of the skin are minimized. These

1 inefficiencies, termed "capacitive loss", are described in McNichols et al US
2 Patent 5,047,007. Capacitive loss results because a portion of each pulse is
3 consumed by the process of charging the skin without delivering drug. The
4 shorter the pulse width (and hence the higher the pulsing frequency), the
5 relatively greater is the capacitive loss for each pulse.

6 In a preferred practice, the electrotransport current density during the
7 first segment and the length of the first segment are selected to maintain the
8 higher efficiency species delivery state of the body surface (e.g., skin). This
9 invention also includes the preferred practice of intentionally renewing the
10 highly efficient species delivery state so as to optimize drug delivery efficiency
11 if drug or agent delivery conditions are used which do not periodically renew
12 it. In another preferred practice, the present invention is utilized to deliver
13 drug or agent transdermally, i.e., through intact skin. In yet a further preferred
14 practice, the present invention is used to deliver drug or agent through intact,
15 live, human skin.

16 In this preferred practice of this invention, the precise current density
17 and treatment time period needed to convert untreated skin to a highly
18 transmissive state have been found to be fairly specific to the drug or
19 therapeutic agent to be delivered. However, for the electrotransport delivery
20 of analgesics using a pulsing electrotransport current, a pulse width of at least
21 10 msec at a current density of about 40 μ A/cm², preferably at least about
22 50 μ A/cm² and most preferably at least about 70 μ A/cm² appears to convert
23 the body site so treated to a highly efficient drug transmissive state. This
24 preferred embodiment of the invention arises out of the discovery that
25 electrotransport delivery efficiency is highly dependent (i.e., it is non-constant)
26 at current densities in the range of about 0 to about 30 μ A/cm², is moderately
27 dependent upon current density in the range of about 40 to about 70 μ A/cm²
28 and is relatively independent of current density at current densities in excess
29 of about 70 μ A/cm². This unexpected change in efficiency (in theory,
30 efficiency is not predicted to change with increasing current density) permits

1 electrotransport transdermal delivery of drug with significantly enhanced
2 electrotransport delivery efficiency.

3 A second unexpected result is achieved in this preferred practice of the
4 present invention, i.e., the change of the skin to the higher efficiency
5 transmissive state is non-transitory with the skin remaining in the higher,
6 and more stable, efficiency state for minutes to hours after the initial
7 transformation, even in cases where the subsequently applied
8 electrotransport current density is lowered to a level below I_c or turned off,
9 completely. In other words, when the skin site has been converted to a highly
10 efficient agent transmissive state by applying a pulsing electric current over
11 pulse widths of at least 5 msec, and at or above current density I_c , reduction
12 in applied electrotransport current (and therefore current density) does not
13 cause the skin to immediately return to its initial, lower electrotransport
14 delivery efficiency state. This observation respecting in vivo drug delivery is
15 critically important to electrotransport system design.

16 The term "non-transitory" as used herein, when referring to the high
17 efficiency electrotransport agent delivery state, means of sufficient length to
18 permit drug to be delivered to achieve a therapeutic effect, generally at
19 least several minutes and preferably at least an hour. Thus, for example,
20 a relatively inexpensive ionic species may be used to trigger conversion of,
21 e.g., a skin site, to a highly efficient and more stable ionic species delivery
22 state, and thereafter relatively more expensive drug or agent may be
23 delivered at greater efficiency and stability by electrotransport. Where the
24 drug or agent is inexpensive, it may be used to convert the body delivery site
25 to the highly efficient and more stable state, and thereafter may be delivered
26 with greater efficiency, i.e., at lower current density and at greater stability.

27 The term "high/higher efficiency state" as used herein means
28 conversion of any particular body or skin site to a state in which drug or agent
29 delivery is at least 10% (preferably at least 20%) more efficient than the same
30 skin site prior to conversion in accordance with this invention. Generally, the

1 parameter which will be most reflective of this efficiency increase will be the
2 electrotransport delivery efficiency measured in micrograms of drug delivered
3 per milliamp-hour of applied electrotransport current.

4 The term "more stable efficiency" as used herein means conversion
5 from a state of more variable electrotransport agent delivery efficiency to one
6 of less variability by exposure of the body site to a current density above the
7 critical current density, I_c , for a time period longer than the critical time, t_c .
8 Critical current density for purposes of increased stability, has been found to
9 be as low as about 40 $\mu\text{A}/\text{cm}^2$.

10 The transdermal drug flux achieved by delivering drug at higher
11 electrotransport delivery efficiency (i.e., at electrotransport current densities
12 above the critical level I_c) may in some cases be higher than the flux needed
13 to achieve the desired therapeutic effect. In such cases, it is desirable to
14 reduce the transdermal drug flux, without reducing the electrotransport
15 current density below the critical level I_c , so as to maintain the skin in the high
16 efficiency and high stability transfer state. This problem may be overcome by
17 one or more of the following three methods.

18 The first method of reducing the drug flux without reducing the applied
19 level of electrotransport current, and hence current density, is to deliver the
20 drug using a pulsing electrotransport current, the pulses of current producing
21 a current density above I_c , and adjusting the pulse width of the current pulses
22 (i.e., adjusting the duty cycle) in order to control the drug delivery rate. The
23 term "duty cycle" as used herein is the ratio of the first period length (in msec)
24 to the sum of the lengths of the first and second periods and is usually
25 expressed as a percent. In other words, the duty cycle is the ratio of pulse
26 width to cycle length. For example, if a device applies current pulses of 500
27 msec duration at a pulsing frequency of 1 pulse per second (i.e., 1 Hz), then
28 the device is operating in a 50% duty cycle. In general, pulsing
29 electrotransport currents typically have duty cycles of 10 to 95%, more
30 typically 20 to 90%, and most typically 30 to 90%. In this practice of the

1 invention, the magnitude of the current pulses is selected in view of the
2 known area of the surface from which drug is delivered, thereby defining a
3 fixed and known current density (i.e., the ratio of current to the area from
4 which current flows). Thus, if it is decided, based upon application of the
5 above principles, that a specific maximum current for a given anode surface
6 area e.g., I_{max} will provide the enhanced efficiency drug delivery discussed
7 above, then by increasing or decreasing the duty cycle, the amount of drug
8 delivered at the high efficiency state can be increased or decreased without
9 causing the applied current density to change. In choosing the parameters of
10 drug delivery if using this approach, the magnitude of the current pulses is
11 selected so that the resulting current density transforms the skin into the high
12 efficiency state and the duty cycle of the current pulses is altered to adjust the
13 drug delivery rate (i.e., a low dose of drug is administered by a high density
14 (i.e., greater than I_c) pulsing current having a shorter pulse width, and hence a
15 low duty cycle and a high dose of drug is administered by the same
16 magnitude current density but being pulsed at a longer pulse width
17 corresponding to a higher duty cycle.

18 This aspect of the invention is more specifically illustrated in FIG. 2
19 where waveforms for three different pulsing electrotransport currents of the
20 same frequency are shown. In FIG. 2 time is illustrated on the horizontal axis,
21 while current amplitude is illustrated on the vertical axis. The three current
22 waveforms shown in FIG. 2 all have the same magnitude, and hence the
23 same maximum applied current density I_{max} for an electrotransport delivery
24 device of any one size. This particular current density I_{max} is greater than the
25 critical current density level I_c . The three current waveforms have differing
26 duty cycles, which is the percentage of time during which the current is
27 applied. The three waveforms have duty cycles of 75% (top waveform),
28 50% (middle waveform) and 25% (bottom waveform). Thus, the 25% duty
29 cycle waveform delivers drug transdermally by electrotransport at about

1 one-half the dosing level of the 50% duty cycle waveform and about one-third
2 the dosing level of the 75% duty cycle waveform. All three waveforms
3 administer drug transdermally by electrotransport through skin which is
4 transformed into the high efficiency transfer state by reason of I_{max} being
5 greater than I_c .

6 The second method of reducing the drug flux without reducing the
7 applied level of electrotransport current, and hence current density, is to
8 deliver the drug using a pulsing electrotransport current, the pulses of current
9 producing a current density above I_c , and maintaining the pulse amplitude
10 and pulse width constant while adjusting the pulsing frequency in order to
11 control the drug delivery rate. In this manner, current density is maintained at
12 or above the level which transforms the skin into the high efficiency state.

13 Exemplary of this, a device employing a pulsed current waveform having
14 current pulses with a magnitude of 0.2 mA, a pulse width of 10 msec, and a
15 frequency of 10 Hz will deliver roughly half as much drug as the same device
16 run at a frequency of 20 Hz. Given a constant drug delivery area, e.g., of an
17 electrode assembly, the applied current densities of these two devices is the
18 same and is above the high efficiency critical level I_c so that both devices
19 deliver drug transdermally by electrotransport with higher efficiency and lower
20 variability compared to devices which apply electrotransport current at current
21 densities below the critical level I_c . From these two examples of the invention,
22 one skilled in this art will appreciate that a combination of frequency and duty
23 cycle may be used to alter the rate of drug delivery while maintaining the first
24 average magnitude sufficient high to produce a current density above I_c . FIG.
25 4 shows the waveforms for a device operated to have a constant 9 msec
26 pulse width, the frequency for a device operated according to the lower
27 waveform being one-half that of a device operated according to the upper
28 waveform (i.e., 50 Hz versus 100 Hz).

29 The third method of reducing the drug flux without reducing the applied
30 level of electrotransport current, and hence current density, is to intentionally

1 deliver competitive co-ions (i.e., ionic species having a charge like that of the
2 therapeutic agent, but which species do not induce a therapeutic effect when
3 delivered into a patient) together with the desired drug so that some portion
4 of the applied electrotransport current is carried by the co-ions rather than the
5 drug ions. Delivery of competitive co-ions, for a given current, in addition to
6 the drug or agent ions, provides adequate current density but reduces the
7 quantity of therapeutic agent delivered. Delivery of competitive co-ions from,
8 e.g., the drug reservoir, also reduces potentially expensive and potent total
9 drug or agent delivered. This approach, under the specific conditions
10 described, permits drug dosage control as well as providing enhanced
11 stability of electrotransport therapeutic agent delivery efficiency. This
12 approach is generally discouraged in the patent literature because it
13 otherwise tends to reduce drug delivery efficiency. This aspect of this
14 invention is particularly applicable to electrotransport delivery of those drugs
15 or therapeutic agents which are therapeutically effective when (i) delivered at
16 low transdermal fluxes and/or (ii) when present in low concentrations in the
17 blood. Generally speaking, this aspect of the present invention is particularly
18 applicable to the electrotransport delivery of highly potent drugs or other
19 therapeutic agents.

20 The competitive ionic species can be loaded into the donor reservoir
21 (e.g., a biocompatible salt is added to the donor reservoir) before
22 electrotransport agent delivery and/or can be generated *in situ* during
23 the operation of the electrotransport device. Generation of competitive
24 ionic species *in situ* may be accomplished using a secondary electrode
25 and appropriate electrical control circuitry as described in Phipps et al
26 US Patent 5,443,442 for example.

27 The amount of the competitive species intentionally added to the donor
28 reservoir will be specific to the drug or agents to be delivered and the relative
29 electrophoretic mobilities of the drug ions and the competing ionic species.
30 Generally, the competitive species will be ionic and should have delivery

1 characteristics similar to those of the drug being delivered. The quantity of
2 co-delivered species to be added is selected so that the total current density
3 is raised above the critical current density, I_c , where the ionic species
4 efficiency is normalized or stabilized so that variation of delivery efficiency is
5 no longer experienced.

6 The teachings in Theeuwes et al US Patent 5,080,646 may be utilized
7 in determining the proper amount of competitive co-ion species to be added
8 to the donor reservoir of an electrotransport delivery device. The patent
9 discusses the processes involved in the transport of species through a
10 biological surface such as skin, mucosa, or tissue. The Theeuwes et al
11 Patent provides a mathematical analysis which permits one skilled in this art,
12 when unacceptable random variability of electrically-assisted drug flux is
13 experienced, to select a suitable quantity and species of competitive co-ion to
14 be delivered along with the drug or agent.

15 Another way to use an inexpensive ionic species to transform the skin
16 into the higher efficiency transfer state is to utilize a reverse polarity system
17 wherein the electric current is initially applied at a level sufficient to produce a
18 current density at or above I_c but which current carries the opposite polarity
19 used to deliver the drug. In this way, the skin can be transferred into the
20 higher/more stable efficiency state with application of current with little or no
21 associated delivery of drug. Once the skin is transformed, the polarity of the
22 applied electrotransport is then returned to the normal polarity used for drug
23 delivery. One example of such a system has an anodic donor reservoir
24 containing a cationic drug (D^+) with an anionic counter ion (X^-) such as
25 chloride. The applied electrotransport current polarity is initially set to drive
26 the counter ion X^- from the donor reservoir for at least the critical time, t_c ,
27 required to transform the skin to the high efficiency/stability state. Once the
28 skin is transformed, the polarity of the applied current is reversed to deliver
29 the drug cation D^+ from the donor reservoir into the skin.

1 As is noted above, agent delivery efficiency is preferably increased by
 2 exposure of the site to a current density at or above I_c and for a time period
 3 equal to or greater than a critical time, t_c . Generally speaking, for a pulsing
 4 electrotransport device, the pulse width (i.e., the length of the first segment of
 5 the waveform) must equal or exceed t_c . Thus, t_c , in a practice of this invention
 6 using pulsed current electrotransport devices and for delivery of fentanyl, falls
 7 between about 0.5 msec and 30 msec. It is believed that the minimum pulse
 8 width to cause transformation to the higher efficiency state is about 10 msec
 9 for fentanyl.

10 Table 1 shows data which support the above observation. Table 1
 11 shows drug delivery efficiency data for a device programmed to run at
 12 frequencies of 1 Hz, 10 Hz and 625 Hz. A 31% duty cycle was employed.

13

14

TABLE 1

15

Frequency (Hz)	Pulse Width (msec)	Rate of Fentanyl Delivery (μ g/hr)	
		Without Bolus Treatment	After Bolus Treatment*
625	0.5	7	34
10	31	52**	52**
1	310	48**	48**

16

17 * "Bolus Treatment" means a direct current bolus delivery of fentanyl for
 18 a period of 30 minutes at a current density of 0.1mA/cm^2 .

19

20 ** The numbers in these two columns are the same because even at a
 21 pulse width as short as 31 msec, the skin site had already transformed
 22 to its highly efficient state.

23

24

25 Table 1 also indicates that fentanyl delivery is significantly lower at a
 26 high pulsing frequency of 625 Hz compared to the lower pulsing frequencies

1 of 1 and 10 Hz. This phenomenon is called capacitive loss, which loss
2 becomes greater as pulsing frequency is increased at a given duty cycle.
3 Table 1 also shows that until a critical pulse width is achieved, regardless of
4 frequency, no transformation of the body site agent delivery efficiency occurs.

5 Pulsed current electrotransport devices are well known in the art.
6 Such devices are described in numerous technical articles and the patent
7 literature including Bagniefski et al "A Comparison of Pulsed and Continuous
8 Current Iontophoresis", Journal of Controlled Release, 113-122, (1090);
9 McNichols et al, US patent 5,047,007; Sibalis US Patent 5,135,478; R.
10 Burnette et al "Influence of Constant Current Iontophoresis on the Impedance
11 and Passive Na^+ Permeability of Excised Nude Mouse Skin", 77
12 J.Pharmaceutical Sciences 492 (1988); Pikal et al, "Study of the Mechanisms
13 of Flux Enhancement Through Hairless Mouse Skin by Pulsed DC
14 Iontophoresis," 8 Pharmaceutical Research 365 (1991).

15 In a preferred aspect of the present invention, the efficiency (E) of
16 transdermal electrotransport drug delivery is, at least at lower applied
17 electrotransport current densities, dependent on the applied electrotransport
18 current density (I_d). This phenomenon is illustrated graphically in FIG. 1.
19 Specifically, when electrotransport current densities above a critical current
20 density level, I_c , are applied to the skin of living animals for sufficient periods
21 of time longer than a critical period of time, t_c , on the order of several
22 milliseconds, the drug delivery efficiency (E) increases to a plateau level and
23 is no longer dependent upon the level of applied current density. It is
24 important to note that the variable electrotransport delivery efficiency effect is
25 a limited exception to the widely reported principle that transdermal
26 electrotransport drug flux is linearly dependent upon the level of applied
27 electrotransport current. Our discovery is that this principle is only true at
28 current densities above a critical current density level I_c . Thus, we have
29 discovered that, at applied current densities below the critical current density
30 level I_c , the rate of electrotransport drug delivery per unit of applied

1 electrotransport current is not constant as has been previously assumed. Not
2 only is the electrotransport drug delivery efficiency (E) lower at current
3 densities below I_c , E also exhibits greater variability at current densities below
4 I_c than at current densities above the critical level I_c . Thus, at applied current
5 densities below I_c , the electrotransport delivery is less efficient in that more
6 electrotransport current must be applied to deliver a predetermined amount of
7 drug. A still further aspect of our discovery is that the interpatient variability in
8 transdermal electrotransport efficiency is lower at applied current densities
9 above the critical level I_c and higher at applied current density levels below
10 the critical level I_c .

11 In general, the critical current density level I_c for human skin is in the
12 range of about 40 to 100 $\mu\text{A}/\text{cm}^2$, although the critical level I_c will vary
13 somewhat depending upon (i) the particular drug being delivered,
14 (ii) the particular patient being treated, and (iii) the particular skin location of
15 the patient wearing the electrotransport device. Typically, a current density at
16 or above the critical level I_c need only be applied for several milliseconds to
17 several seconds before the skin enters the high efficiency drug transfer state.
18 However, applied current densities below the critical level I_c are unable to
19 transform the skin into the high efficiency transfer state, even when these low
20 level current densities are applied for extended periods of time (e.g., up to
21 several hours application). This transformation of the skin to a higher
22 efficiency delivery state occurs only in living animals and does not occur with
23 excised skin taken from living or dead animals, i.e.,
24 the skin transformation has not been found to occur when in vitro flux studies
25 were run.

26 Once the skin has been transformed into the high efficiency
27 transfer state, it tends to remain in that state for an extended period of time
28 (e.g., up to 24 hours) even if no further electrotransport current is thereafter
29 applied to the skin or if only low level current densities (i.e., current densities
30 less than the critical level I_c) are thereafter applied to the skin. This result is

1 illustrated in FIG. 5 and is discussed below. The "transformed" skin is in
2 general only those skin sites which are in contact with the donor and counter
3 electrodes/reservoirs of the electrotransport delivery device and through
4 which skin sites the applied current has been passed. Thus, if a skin site on
5 the upper arm of a patient has been transformed by application of
6 electrotransport current densities above the critical level I_c , the skin on the
7 lower (same) arm, the legs, torso or other arm of the patient does not
8 become transformed. The skin transformation of this invention is a
9 localized phenomenon which is limited to those portions of the skin to
10 which the donor and counter electrodes/reservoirs are attached. Since the
11 skin at the counter electrode site also is converted to the high efficiency
12 delivery state, methods and devices for delivering agents from the "donor"
13 and "counter" electrodes, or both (e.g., by alternating current polarity)
14 are within the scope of this invention.

15 Our discovery is particularly critical in those transdermal
16 electrotransport drug delivery regimens wherein the drug is delivered at two
17 (or more) different dosing levels, one dosing level being administered at a
18 current density below the critical level I_c and another dosing level being
19 administered at a current density above the critical level. For example,
20 many drugs are adapted to be administered at a low dose baseline rate for
21 extended periods, the baseline rate being interrupted periodically by periods
22 of higher dosing. Examples of drugs which are administered in this fashion
23 include (1) analgesics, such as fentanyl and sufentanil, which are
24 administered at a low baseline level to treat (e.g., chronic) pain and which are
25 periodically delivered at higher doses to treat more severe episodes of pain;
26 (2) anti-emetics, such as the 5HT3 receptor antagonists ondansetron and
27 granisetron, which are administered continuously at low levels (e.g., during
28 weeks over which a patient is undergoing chemotherapy) and which are
29 periodically administered at higher dosing levels (i.e., during the actual
30 chemotherapeutic administration); (3) anti-epileptics, such as phenytoin,

1 which are delivered continuously at low baseline levels and periodically at
2 higher levels when the patient is undergoing an epileptic seizure; and
3 (4) anti-diabetic drugs, such as insulins, which can be delivered continuously
4 at low baseline levels and periodically (e.g., just before, during or after meals)
5 at higher levels. The problem encountered with this type of transdermal
6 electrotransport drug administration is that after the drug is administered at
7 the higher dosing rate (with the applied current density above the critical level,
8 I_c), when the applied electrotransport current is readjusted to apply the
9 original lower baseline level, the transdermal electrotransport drug flux does
10 not return to the same baseline level. The drug flux instead falls to a level
11 somewhere between the original baseline rate and the high dosing rate,
12 because the skin has been transformed into a higher efficiency drug delivery
13 state. For example, if the efficiency is enhanced by a factor of two, after the
14 skin has experienced a current density above the critical current density,
15 and then the current is lowered to the original base line current, the drug
16 delivery rate would be twice that experienced before the transformation.
17 The higher baseline rate could result in a drug overdose if the electrotransport
18 system does not compensate for this shift in efficiency. To eliminate this
19 problem, the electrotransport system should reduce the current applied (e.g.,
20 by approximately a factor of two) after the skin has experienced a current
21 density greater than I_c . With reference to FIG. 1, data point 2 is a likely
22 efficiency that would be experienced at the drug delivery site were current
23 (and therefore current density) reduced after exposure of the body site to
24 current density at or above I_c for at least a period of time t_c . At data point "2"
25 electrotransport agent delivery efficiency is higher than the agent delivery
26 efficiency which was initially experienced at a current density of about 20
27 $\mu\text{A}/\text{cm}^2$ (i.e., at a time before exposure of the skin to a current density above
28 I_c).
29 Reference is now made to FIG. 3 which depicts an exemplary
30 electrotransport device which can be used in accordance with the present

1 invention. FIG. 3 shows a perspective exploded view of an electrotransport
2 device 10 having an activation switch in the form of a push button switch 12
3 and a display in the form of a light emitting diode (LED) 14. Device 10
4 comprises an upper housing 16, a circuit board assembly 18, a lower housing
5 20, anode electrode 22, cathode electrode 24, anode reservoir 26, cathode
6 reservoir 28 and skin-compatible adhesive 30. Upper housing 16 has lateral
7 wings 15 which assist in holding device 10 on a patient's skin. Upper
8 housing 16 is preferably composed of an injection moldable elastomer
9 (e.g., ethylene vinyl acetate). Printed circuit board assembly 18 comprises
10 an integrated circuit 19 coupled to discrete electrical components 40 and
11 battery 32. Circuit board assembly 18 is attached to housing 16 by posts
12 (not shown in FIG. 3) passing through openings 13a and 13b, the ends
13 of the posts being heated/melted in order to heat stake the circuit board
14 assembly 18 to the housing 16. Lower housing 20 is attached to the upper
15 housing 16 by means of adhesive 30, the upper surface 34 of adhesive 30
16 being adhered to both lower housing 20 and upper housing 16 including the
17 bottom surfaces of wings 15.

18 Shown (partially) on the underside of circuit board assembly 18 is a
19 battery 32, which is preferably a button cell battery and most preferably a
20 lithium cell. Other types of batteries, such as sizes AAA and AAAA may also
21 be employed to power device 10.

22 The circuit outputs (not shown in FIG. 3) of the circuit board assembly
23 18 make electrical contact with the electrodes 24 and 22 through openings
24 23,23' in the depressions 25,25' formed in lower housing, by means of
25 electrically conductive adhesive strips 42,42'. Electrodes 22 and 24, in turn,
26 are in direct mechanical and electrical contact with the top sides 44',44 of
27 drug reservoirs 26 and 28. The bottom sides 46',46 of drug reservoirs 26,28
28 contact the patient's skin through the openings 29',29 in adhesive 30. Upon
29 depression of push button switch 12, the electronic circuitry on circuit board
30 assembly 18 delivers a predetermined DC current to the electrodes/reservoirs

1 22,26 and 24,28 for a delivery interval of predetermined length, e.g., about 10
2 minutes. Preferably, the device transmits to the user a visual and/or audible
3 confirmation of the onset of the drug delivery, or bolus, interval by means of
4 LED 14 becoming lit and/or an audible sound signal from, e.g., a "beeper".
5 Drug (e.g., an analgesic drug such as fentanyl) is then delivered through the
6 patient's skin, e.g., on the arm, for the predetermined delivery interval. In
7 practice, a user receives feedback as to the onset of the drug delivery interval
8 by visual (LED 14 becomes lit) and/or audible signals (a beep from the
9 "beeper"). A preferred device is described in commonly owned, pending
10 patent application entitled "Display for an Electrotransport Device", US Patent
11 Application Serial Number 08/410,112, filed March 24, 1995.

12 Anodic electrode 22 is preferably comprised of silver and cathodic
13 electrode 24 is preferably comprised of silver chloride. Both reservoirs 26
14 and 28 are preferably comprised of polymer hydrogel materials as described
15 herein. Electrodes 22, 24 and reservoirs 26, 28 are retained by lower housing
16 20. When the drug being delivered by electrotransport is cationic, the anodic
17 reservoir 26 is the "donor" reservoir which contains the drug and the cathodic
18 reservoir 28 contains a biocompatible electrolyte. When the drug being
19 delivered by electrotransport is anionic, the cathodic reservoir 28 is the
20 "donor" reservoir which contains the drug and the anodic reservoir 26
21 contains a biocompatible electrolyte.

22 The push button switch 12, the electronic circuitry on circuit board
23 assembly 18 and the battery 32 are adhesively "sealed" between upper
24 housing 16 and lower housing 20. Upper housing 16 is preferably composed
25 of rubber or other elastomeric material. Lower housing 20 is preferably
26 composed of a plastic or elastomeric sheet material (e.g., polyethylene)
27 which can be easily molded to form depressions 25,25' and cut to form
28 openings 23,23'. The assembled device 10 is preferably water resistant
29 (i.e., splash proof) and is most preferably waterproof. The system has a low
30 profile that easily conforms to the body thereby allowing freedom of

1 22,26 and 24,28 for a delivery interval of predetermined length, e.g., about 10
2 minutes. Preferably, the device transmits to the user a visual and/or audible
3 confirmation of the onset of the drug delivery, or bolus, interval by means of
4 LED 14 becoming lit and/or an audible sound signal from, e.g., a "beeper".
5 Drug (e.g., an analgesic drug such as fentanyl) is then delivered through the
6 patient's skin, e.g., on the arm, for the predetermined delivery interval. In
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18 reservoir 28 contains a biocompatible electrolyte. When the drug being
19 delivered by electrotransport is anionic, the cathodic reservoir 28 is the
20 "donor" reservoir which contains the drug and the anodic reservoir 26
21 contains a biocompatible electrolyte.

22 The push button switch 12, the electronic circuitry on circuit board
23 assembly 18 and the battery 32 are adhesively "sealed" between upper
24 housing 16 and lower housing 20. Upper housing 16 is preferably composed
25 of rubber or other elastomeric material. Lower housing 20 is preferably
26 composed of a plastic or elastomeric sheet material (e.g., polyethylene)
27 which can be easily molded to form depressions 25,25' and cut to form
28 openings 23,23'. The assembled device 10 is preferably water resistant
29 (i.e., splash proof) and is most preferably waterproof. The system has a low
30 profile that easily conforms to the body thereby allowing freedom of

1 movement at, and around, the wearing site. The anode reservoir 26 and the
2 cathode reservoir 28 are located on the skin-contacting side of device 10 and
3 are sufficiently separated to prevent accidental electrical shorting during
4 normal handling and use.

5 The device 10 adheres to the patient's body surface (e.g., skin) by
6 means of a peripheral adhesive 30 which has upper side 34 and body-
7 contacting side 36. The adhesive side 36 has adhesive properties which
8 assures that the device 10 remains in place on the body during normal user
9 activity, and yet permits reasonable removal after the predetermined
10 (e.g., 24-hour) wear period. Upper adhesive side 34 adheres to lower
11 housing 20 and retains the electrodes and drug reservoirs within housing
12 depressions 25,25' as well as retains lower housing 20 attached to upper
13 housing 16.

14 The push button switch 12 is located on the top side of device 10 and
15 is easily actuated through clothing. A double press of the push button switch
16 12 within a short period of time, e.g., three seconds, is preferably used to
17 activate the device 10 for delivery of drug, thereby minimizing the likelihood of
18 inadvertent actuation of the device 10.

19 Upon switch activation an audible alarm signals the start of drug
20 delivery, at which time the circuit supplies a predetermined level of
21 DC current to the electrodes/reservoirs for a predetermined delivery interval.
22 The LED 14 remains "on" throughout the delivery interval indicating that the
23 device 10 is in an active drug delivery mode. The battery preferably has
24 sufficient capacity to continuously power the device 10 at the predetermined
25 level of DC current for the entire wearing period.

26 The present invention is particularly useful in the transformation of
27 human skin in the transdermal electrotransport delivery of drugs to humans.
28 However, the invention also has utility in delivering drugs to other animals and
29 is not limited to humans.

1 The terms "agent" and "drug" are used interchangeably herein and are
2 intended to have their broadest interpretation as any therapeutically active
3 substance which is delivered to a living organism to produce a desired,
4 usually beneficial, effect. In general, this includes therapeutic agents in all of
5 the major therapeutic areas including, but not limited to, anti-infectives such
6 as antibiotics and antiviral agents, analgesics and analgesic combinations,
7 anesthetics, anorexics, antiarthritics, antiasthmatic agents, anticonvulsants,
8 anti-depressants, antidiabetic agents, antidiarrheals, antihistamines, anti-
9 inflammatory agents, antimigraine preparations, antimotion sickness
10 preparations, antinauseants, antineoplastics, antiparkinsonism drugs,
11 antipruritics, antipsychotics, antipyretics, antispasmodics including
12 gastrointestinal and urinary antispasmodics, anticholinergics,
13 sympathomimetics, xanthine derivatives, cardiovascular preparations
14 including calcium channel blockers, beta-blockers, antiarrhythmics,
15 antihypertensives, diuretics, vasodilators including general, coronary,
16 peripheral and cerebral vasodilators, central nervous system stimulants,
17 cough and cold preparations, decongestants, diagnostics, hormones,
18 hypnotics, immunosuppressives, muscle relaxants, parasympatholytics,
19 parasympathomimetics, proteins, peptides, polypeptides and other
20 macromolecules, psychostimulants, sedatives and tranquilizers.

21 The present invention can be used to deliver transdermally by
22 electrotransport the following drugs: interferons, alfentanyl, amphotericin B,
23 angiopeptin, baclofen, beclomethasone, betamethasone, bisphosphonates,
24 bromocriptine, buserelin, buspirone, calcitonin, ciclopirox, olamine, copper,
25 cromolyn sodium, desmopressin, diclofenac diflorasone, diltiazem,
26 dobutamine, dopamine agonists, dopamine agonists, doxazosin, droperidol,
27 enalapril, enalaprilat, fentanyl, encainide, G-CSF, GM-CSF, M-CSF, GHRF,
28 GHRH, gonadorelin, goserelin, granisetron, haloperidol, hydrocortisone,
29 indomethacin, insulin, insulinotropin, interleukins, isosorbide dinitrate,
30 ketoprofen, ketorolac, leuprolide, LHRH, lidocaine, lisinopril, LMW heparin,

1 melatonin, methotrexate, metoclopramide, miconazole, midazolam, nafarelin,
2 nicardipine, NMDA antagonists, octreotide, ondansetron, oxybutynin, PGE₁,
3 piroxicam, pramipexole, prazosin, prednisolone, prostaglandins, scopolamine,
4 seglitide, sufentanil, terbutaline, testosterone, tetracaine, tropisetron,
5 vapreotide, vasopressin, verapamil, warfarin, zacopride, zinc, and zotasetron.

6 This invention is also believed to be useful in the transdermal
7 electrotransport delivery of peptides, polypeptides and other macromolecules
8 typically having a molecular weight of at least about 300 daltons, and typically
9 a molecular weight in the range of about 300 to 40,000 daltons. Specific
10 examples of peptides and proteins in this size range include, without
11 limitation, LHRH, LHRH analogs such as buserelin, gonadorelin, nafarelin and
12 leuprolide, GHRH, insulin, heparin, calcitonin, endorphin, TRH, NT-36
13 (chemical name: N=([(s)-4-oxo-2-azetidinyl]carbonyl]-L-histidyl-L-
14 prolinamide), liprecin, pituitary hormones (e.g., HGH, HMG, HCG,
15 desmopressin acetate, etc.), follicle luteoids, α ANF, growth hormone
16 releasing factor (GHRF), β MSH, TGF- β , somatostatin, atrial natriuretic
17 peptide, bradykinin, somatotropin, platelet-derived growth factor,
18 asparaginase, bleomycin sulfate, chymopapain, cholecystokinin, chorionic
19 gonadotropin, corticotropin (ACTH), epidermal growth factor, erythropoietin,
20 epoprostenol (platelet aggregation inhibitor), follicle stimulating hormone,
21 glucagon, hirulogs, hyaluronidase, interferons, insulin-like growth factors,
22 interleukins, menotropins (urofollitropin (FSH) and LH), oxytocin,
23 streptokinase, tissue plasminogen activator, urokinase, vasopressin, ACTH
24 analogs, ANP, ANP clearance inhibitors, angiotensin II antagonists,
25 antidiuretic hormone agonists, antidiuretic hormone antagonists, bradykinin
26 antagonists, CD4, ceredase, CSF's, enkephalins, FAB fragments, IgE peptide
27 suppressors, IGF-1, neuropeptide Y, neurotrophic factors, opiate peptides,
28 parathyroid hormone and agonists, parathyroid hormone antagonists,
29 prostaglandin antagonists, pentigetide, protein C, protein S, ramoplanin, renin

1 inhibitors, thymosin alpha-1, thrombolytics, TNF, vaccines, vasopressin
2 antagonist analogs, alpha-1 anti-trypsin (recombinant).
3 Generally speaking, it is most preferable to use a water soluble form of
4 the drug or agent to be delivered. Drug or agent precursors, i.e., species
5 which generate the selected species by physical or chemical processes such
6 as ionization, dissociation, dissolution or covalent chemical modification
7 (i.e., prodrugs), are within the definition of "agent" or "drug" herein. "Drug" or
8 "agent" is to be understood to include charged and uncharged species as
9 described above.

10 While the disclosure has focused upon the electrotransport delivery of
11 ionic species, the present invention is also applicable to the electrotransport
12 delivery of uncharged species, e.g., by electroosmosis. Thus, the
13 transformation of the skin into the high efficiency transport state is not limited
14 to electrically assisted transport of ionic species but also to electroosmotic
15 delivery of uncharged (i.e., non-ionized) species.

16 The following examples illustrate some of the advantages of the
17 present invention.

EXAMPLE 1

20 Pulsing Frequency and Fentanyl Flux

22 This study assessed the effect of pulsing frequency on the
23 electrotransport delivery of fentanyl using pulsed current waveforms.
24 The frequencies evaluated in this study were 1, 10, and 625 Hz.

25 The electrotransport devices were configured to deliver a 200 μ A
26 square wave current pulse, having a 31% duty cycle. At the frequency of
27 1 Hz, the 31% duty cycle square wave current achieved a current pulse width
28 of 310 msec. At the frequency of 10 Hz, the 31% duty cycle square wave
29 current achieved a current pulse width of 31 msec. At the frequency of 625
30 Hz, the 31% duty cycle square wave current achieved a current pulse

1 width of 0.5 msec. The electrotransport devices delivered fentanyl through
2 the skin from a donor hydrogel having a skin contact surface area of 2 cm².
3 Thus, the applied maximum current density, I_{max} , was 100 μ A/cm²
4 (200 μ A \div 2 cm² = 100 μ A/cm²). The gels were imbibed with an aqueous
5 solution of fentanyl HCl. After treatment periods of varying duration,
6 the electrotransport devices were removed. The skin site was then washed
7 to remove any residual fentanyl.

8 For each treatment, blood samples were taken commencing with the
9 application of current from the electrotransport devices. Serum fentanyl
10 levels from each patient were used to calculate mean drug flux.

11 FIG. 7 shows that the use of a square-wave frequency of 625 Hz
12 resulted in minimal fentanyl flux. This is shown in the lower most nearly
13 horizontal curve in FIG. 7. The use of the lower pulsing frequencies, 1 and 10
14 Hz, resulted in increased fentanyl flux. This is shown in the upper two curves
15 of FIG. 7. No statistically significant difference in fentanyl flux was observed
16 between 1 and 10 Hz. These results suggest that the use of lower pulsing
17 frequencies results in higher electrotransport delivery efficiency of fentanyl.

18 The remaining Examples do not utilize a pulsing electrotransport
19 current, and are therefore relevant only to the preferred aspect of the present
20 invention wherein the applied current density (of each of the pulses) is
21 maintained above I_c .

22

23 **EXAMPLE 2**

24

25 **Current Density and Increased Efficiency**

26

27 This study evaluated the effect of applied current density on
28 electrotransport drug delivery efficiency. Drug delivery efficiency is expressed
29 in terms of the rate of drug delivery per unit of applied current. The study

1 involved the application of electrotransport devices to eighteen healthy male
2 volunteers for a duration of about one day.

3 The two electrotransport treatments involved the delivery of fentanyl,
4 from a donor reservoir containing an aqueous solution of fentanyl HCl and
5 having a skin-contact area of 5 cm², at a baseline current of 100 µA. Thus,
6 the applied electrotransport current density was 20 µA/cm² (= 100 µA ÷ 5
7 cm²). Six of the eighteen volunteers were administered 4 bolus doses during
8 the first hour of treatment by applying current levels of 1300 µA (i.e., an
9 applied electrotransport current density of 260 µA/cm²) for a duration of 2.5
10 minutes at 15 minute intervals. Following the administration of the four
11 boluses in the first hour of treatment, these six volunteers received
12 continuous transdermal electrotransport fentanyl administration at a current
13 density of 20 µA/cm² from hour 2 through 24 hours. The remaining twelve
14 volunteers received continuous transdermal electrotransport fentanyl
15 administration at a current density of 20 µA/cm² over the entire 24 hour
16 delivery period. After the treatment period, the electrotransport devices were
17 removed. The skin site was then washed to remove any residual fentanyl.

18 Blood samples were taken over the entire 24 hour period commencing
19 with the application of current from the electrotransport devices. Serum
20 fentanyl concentrations were used to calculate mean transdermal fentanyl
21 fluxes using subject specific pharmacokinetic parameters and conventional
22 methods.

23 FIG. 5 shows that once a skin site receives a minimum level of current
24 (for a fixed electrode area) for a sufficient duration, a high electrotransport
25 efficiency state is achieved. FIG. 5 shows the mean serum fentanyl
26 concentration in the blood of the subjects over the 24 hour testing period.
27 As is shown in the uppermost curve (◊---◊---◊) in FIG. 5, the six volunteers
28 which received the four 260 µA/cm², 2.5 minute bolus administrations in the
29 first hour of treatment exhibited higher efficiency fentanyl transdermal delivery
30 than the group of twelve subjects shown as three groups of four in the three

1 lower curves (to emphasize inherent variability) who received only the 20
2 $\mu\text{A}/\text{cm}^2$ constant DC current. Once this high-efficiency transport state is
3 achieved, more drug is delivered through the skin per unit of applied current.
4 Further, the effect lasted the entire 24 hours of the treatment. This is
5 indicated by the vertical separation between the upper curve and the
6 three lower curves in FIG. 5.

7 Specifically, the six volunteers who received the four $260 \mu\text{A}/\text{cm}^2$
8 doses in the first hour of treatment exhibited a mean transdermal fentanyl flux
9 of $113 \mu\text{g}/\text{h}$ while the twelve volunteers who received only the $20 \mu\text{A}/\text{cm}^2$
10 baseline current exhibited a mean transdermal fentanyl flux of $57 \mu\text{g}/\text{h}$. This
11 indicates that the efficiency was enhanced by about a factor of two as a result
12 of the initial high current density applications.

13

14 EXAMPLE 3

15

16 Current Density and Fentanyl Flux

17

18 This study was undertaken to evaluate the relationship of current
19 density and drug flux in the transdermal electrotransport delivery of fentanyl.
20 Electrotransport devices, delivering constant DC currents, were applied to
21 8 healthy male volunteers for a duration of 24 hours. The three
22 electrotransport treatment regimens in this study differed only in the applied
23 electrotransport current (and therefore current density) levels. The
24 electrotransport devices delivered fentanyl through the skin from a donor
25 hydrogel having a skin contact surface area of 5 cm^2 . The gels were imbibed
26 with an aqueous solution of fentanyl HCl. The current density levels used in
27 this study were $10, 20$, and $40 \mu\text{A}/\text{cm}^2$. After a 24 hour treatment period,
28 the electrotransport devices were removed. The skin site was then washed to
29 remove any residual fentanyl. All 8 volunteers received each treatment
30 approximately 1 week apart.

1 For each treatment, blood samples were taken over a 24 hour period
2 commencing with the application of current from the electrotransport devices.
3 Serum fentanyl concentrations over the 24 hours are shown in FIG. 6.
4 The top curve (-Δ-Δ-Δ-) in FIG. 6 was the 200 μ A treatment (i.e., 40
5 μ A/cm²), the middle curve (-□-□-□-) the 100 μ A treatment (i.e., 20 μ A/cm²)
6 and the bottom curve (-○-○-○-) the 50 μ A treatment (i.e., 10 μ A/cm²).
7 As in Example 2, the serum fentanyl concentrations from each patient were
8 used to calculate mean transdermal fentanyl flux and the mean total amount
9 of fentanyl delivered. A drug delivery efficiency level for each treatment was
10 derived by dividing the mean fentanyl delivery rate by the current density
11 applied to the skin.

12 The average transdermal fentanyl fluxes were 19, 73 and 173 μ g/h at
13 the applied current densities 10, 20 and 40 μ A/cm², respectively. This data
14 shows a non-linear relationship between applied current and transdermal
15 electrotransport fentanyl flux within the electrotransport current density range
16 of 10 to 40 μ A/cm². An almost ten-fold increase in drug delivery rate was
17 observed as the current was increased four-fold from 50 μ A to 200 μ A. This
18 unexpected result indicates that the efficiency of fentanyl delivery was
19 enhanced by a factor of about 2.5-fold due to the change in current density
20 from 10 to 40 μ A/cm².

21

22 EXAMPLE 4

23

24 This study was undertaken to evaluate the relationship between
25 current density and drug flux in the transdermal electrotransport delivery of
26 goserelin. The study involved the application of electrotransport devices,
27 applying constant current, to 12 normal male volunteers for a duration of
28 8 hours.

1 The two electrotransport treatment regimens in this study differed
2 only in applied current density levels. The electrotransport devices delivered
3 goserelin through the skin from polyvinyl alcohol (PVOH)-based donor
4 hydrogels having a skin-contact surface area of 4 cm². The gels contained an
5 aqueous goserelin solution. The current density levels used in this study
6 were 50 and 100 µA/cm². After an 8 hour treatment period, the
7 electrotransport devices were removed. The skin site was then washed to
8 remove any residual goserelin. All 12 volunteers received each treatment
9 seven days apart.

10 For each treatment, seven blood samples were taken over a 24 hour
11 period commencing with the application of current from the electrotransport
12 devices. Serum goserelin concentrations from each patient were used to
13 calculate mean drug flux and the mean total amount of drug delivered.

14 FIG. 8 shows the goserelin blood plasma concentrations for the 8 hour
15 duration of electrotransport administration for the two current densities (i.e.,
16 50 and 100 µA/cm²). The 100 µA/cm² curve is the upper curve in FIG. 8 while
17 the lower curve in FIG. 8 is the 50 µA/cm² data. From this concentration data,
18 transdermal goserelin fluxes were calculated. The average transdermal
19 goserelin flux was 5.8 µg/h at an applied current density of 50 µA/cm² while
20 the average transdermal flux of goserelin was 21.6 µg/h at an applied current
21 density of 100 µA/cm². Thus, a non-linear relationship between applied
22 current density and drug flux was shown by the data. An almost four-fold
23 increase in drug flux is observed as the current density rises from 50 to
24 100 µA/cm². This data also suggests the existence of a critical current
25 density, I_c, which for transdermal electrotransport delivery of goserelin falls
26 between 50 and 100 µA/cm², above which more drug is delivered through the
27 skin per unit of applied current.

28 The above disclosure will suggest many alternatives, permutations,
29 and variations of the invention to one skilled in this art without departing from
30 the scope of the invention. The above disclosure is intended to be illustrative

1 and not exhaustive. All such, permutations, variations, and alternatives
2 suggested by the above disclosure are to be included within the scope of the
3 attached claims.

1 **Claims:**

2

3 1. **An device (10) for delivering a therapeutic agent through a body**
4 **surface by electrotransport, the device (10) having a donor reservoir (26,46)**
5 **containing the therapeutic agent, the donor reservoir (26,46) being adapted to**
6 **be placed in therapeutic agent-transmitting relation with the body surface, the**
7 **device (10) also having a source of electrical power (32) and a current**
8 **controller (19,40), the power source (32) and current controller (19,40) being**
9 **adapted to apply a pulsing electrotransport current to the reservoir (26,46)**
10 **and the body surface, the pulsing electrotransport current having a periodic**
11 **waveform with a first segment of applied electrotransport current having a first**
12 **average current magnitude, and a second segment of applied electrotransport**
13 **current having a second average current magnitude, the second average**
14 **current magnitude being less than the first average current magnitude, the**
15 **device (10) being characterized by:**

16 **the first segment having a length of at least 5 msec.**

17

18 2. **The device of claim 1, wherein the length of the first segment is**
19 **at least 10 msec.**

20

21 3. **The device of claim 1, wherein the electrotransport current has a**
22 **pulsing frequency of less than about 100 Hz.**

23

24 4. **The device of claim 1, wherein the electrotransport current has a**
25 **pulsing frequency of less than about 10 Hz.**

26

27 5. **The device of claim 1, wherein the first segment has a maximum**
28 **current magnitude, which provides a maximum current density I_{max} .**

29

1 6. The device of claim 5, wherein I_{max} is greater than or equal to
2 40 μ A/cm².

3

4 7. The device of claim 1, wherein the first average current
5 magnitude provides an average current density greater than or equal to
6 40 μ A/cm².

7

8 8. The device of claim 1, wherein the device (10) is adapted to be
9 applied to skin of a human patient.

10

11 9. The device of claim 1, wherein the therapeutic agent is fentanyl,
12 the controller (19,40) controls the first average current magnitude to provide
13 an average current density of at least 40 μ A/cm² during the first segment, and
14 the controller (19,40) controls the length of the first segment to at least about
15 10 msec.

16

17 10. The device of claim 1, wherein the therapeutic agent is
18 goserelin, the controller (19,40) controls the first average current magnitude
19 to provide an average current density of at least about 50 μ A/cm² during the
20 first segment, and the controller (19,40) controls the length of the first
21 segment to at least about 10 msec.

22

23 11. The device of claim 1, wherein the controller (19,40) can adjust
24 the relative lengths of the first and second segments in order to vary the
25 therapeutic agent delivery rate.

26

27 12. The device of claim 1, wherein the donor reservoir (26,46)
28 contains an intentionally added competitive co-ion species whereby the
29 device (10) delivers the agent through the body surface at a reduced rate.

1 13. The device of claim 1, wherein the second average current
2 magnitude is substantially zero.

3

4 14. The device of claim 13, wherein the pulsing current has a
5 square waveform shape.

6

7 15. A method of operating an electrotransport delivery device (10)
8 delivering a therapeutic agent through a body surface by electrotransport,
9 including controlling electrotransport current applied by the device (10) to be a
10 pulsing electrotransport current, the pulsing electrotransport current having a
11 periodic waveform with a first segment of applied electrotransport current
12 having a first average current magnitude, and a second segment of applied
13 electrotransport current having a second average current magnitude, the
14 second average current magnitude being less than the first average current
15 magnitude, the method characterized by:

16 controlling the length of the first segment to at least 5 msec.

17

18 16. The method of claim 15, including controlling the length of the
19 first segment to at least 10 msec.

20

21 17. The method of claim 15, wherein the pulsing current has a
22 pulsing frequency of less than about 100 Hz.

23

24 18. The method of claim 15, wherein the pulsing current has a
25 pulsing frequency of less than about 10 Hz.

26

27 19. The method of claim 15, wherein the first segment has a
28 maximum current magnitude, which provides a maximum current density I_{max} .

29

1 20. The method of claim 19, wherein I_{max} is greater than or equal to
2 40 μ A/cm².

3

4 21. The method of claim 16, wherein the first average current
5 magnitude provides a current density greater than or equal to 40 μ A/cm².

6

7 22. The method of claim 16, wherein the agent is fentanyl, the body
8 surface is human skin, the first average current magnitude is controlled to
9 provide an average current density of at least about 40 μ A/cm², and the
10 segment of applied electric current is controlled to be at least about 10 msec.

11

12 23. The method of claim 16, wherein the agent is goserelin, the
13 body surface is human skin, the first average current magnitude is controlled
14 to provide an average current density of at least about 50 μ A/cm², and the
15 segment of applied electric current is controlled to be at least about 10 msec.

16

17 24. The method of claim 16, including the step of adjusting the
18 relative lengths of the first and second segments to vary the therapeutic agent
19 delivery rate.

20

21 25. The method of claim 16, including intentionally adding a
22 competitive co-ion species to the donor reservoir (26,46), whereby the device
23 (10) delivers the therapeutic agent through the body surface at a reduced
24 rate.

25

26 26. The method of claim 16, wherein the second average current
27 magnitude is substantially zero.

28

29 27. The method of claim 26, wherein the pulsing current has a
30 square waveform shape.

FIG. 1

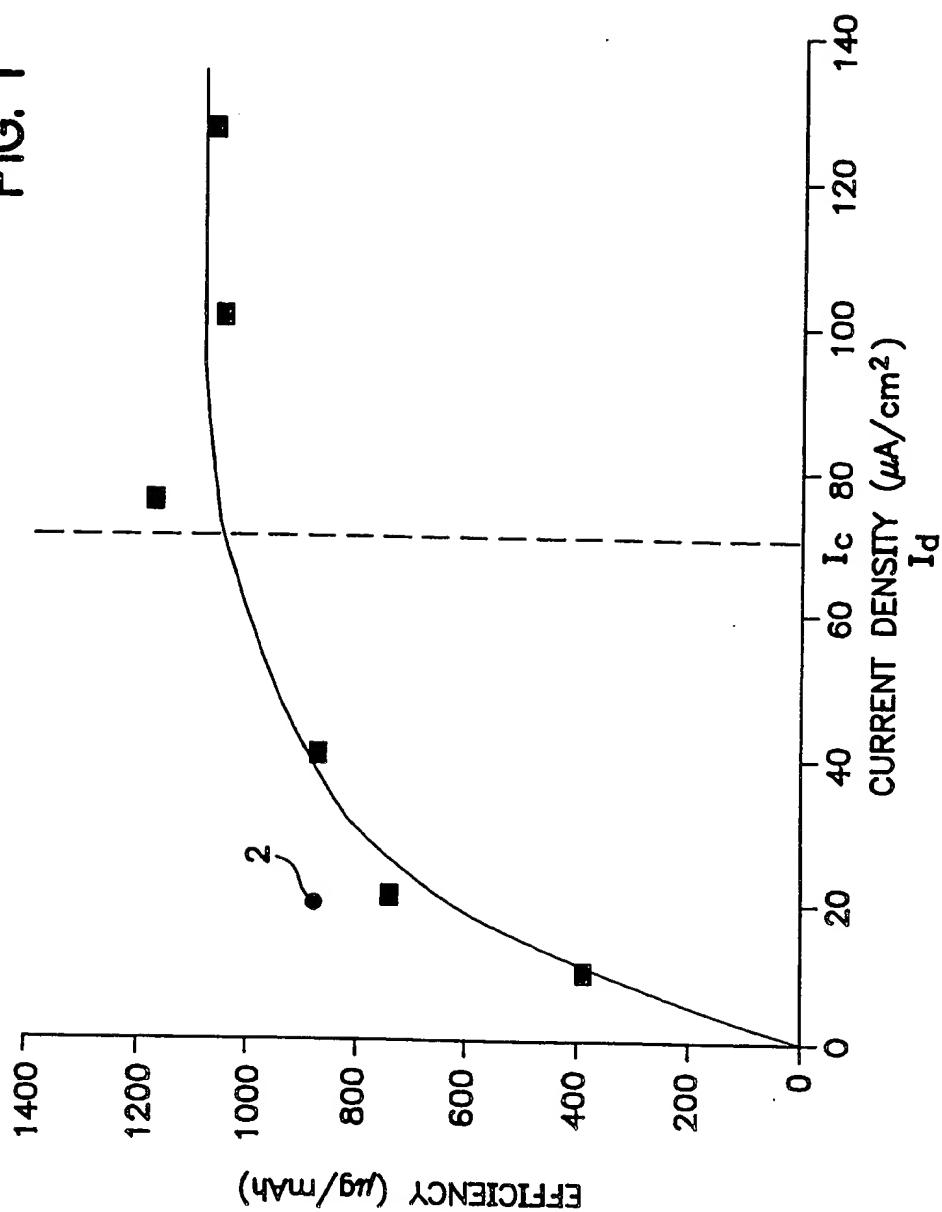
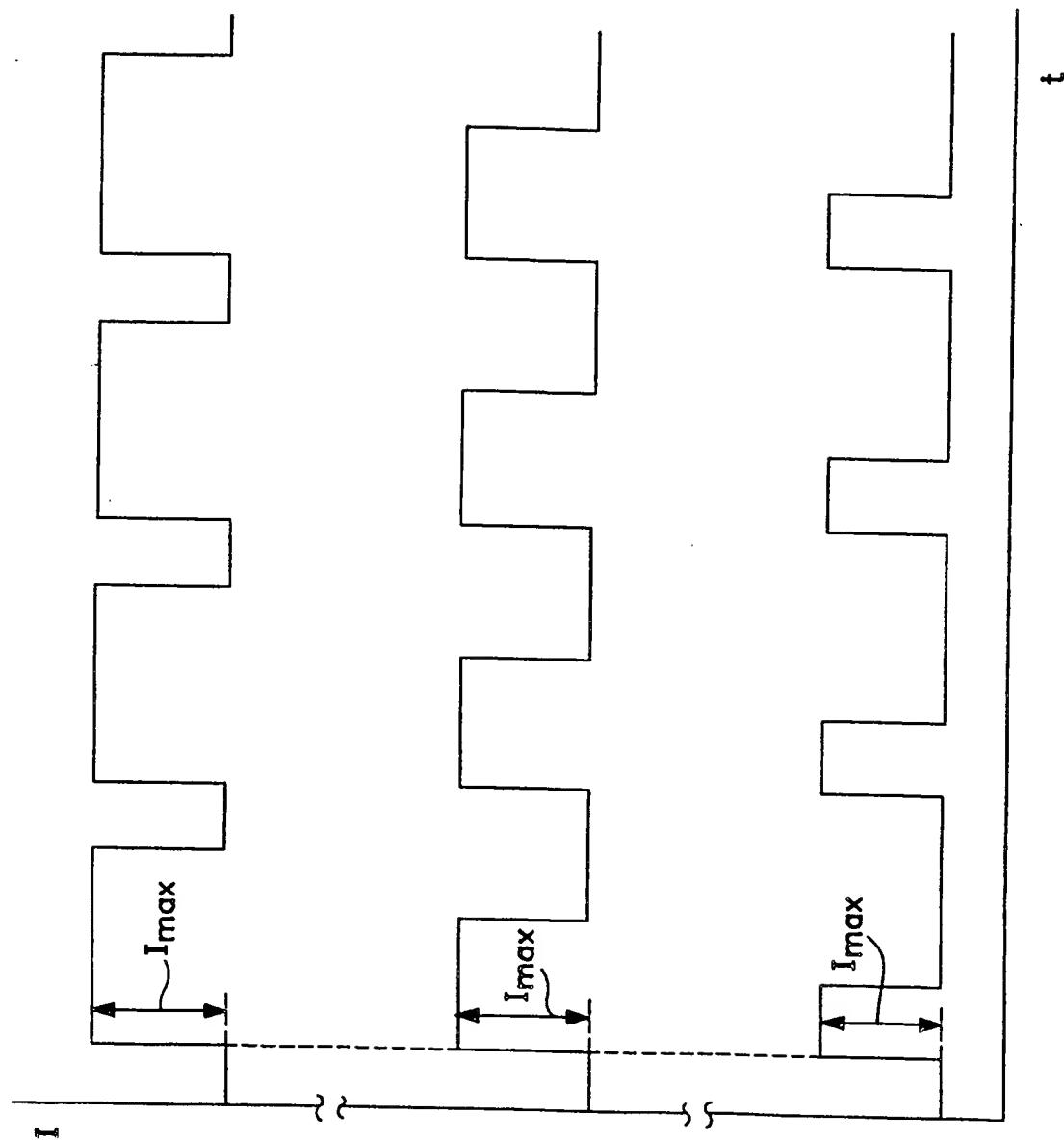


FIG. 2



3 / 8

FIG. 3

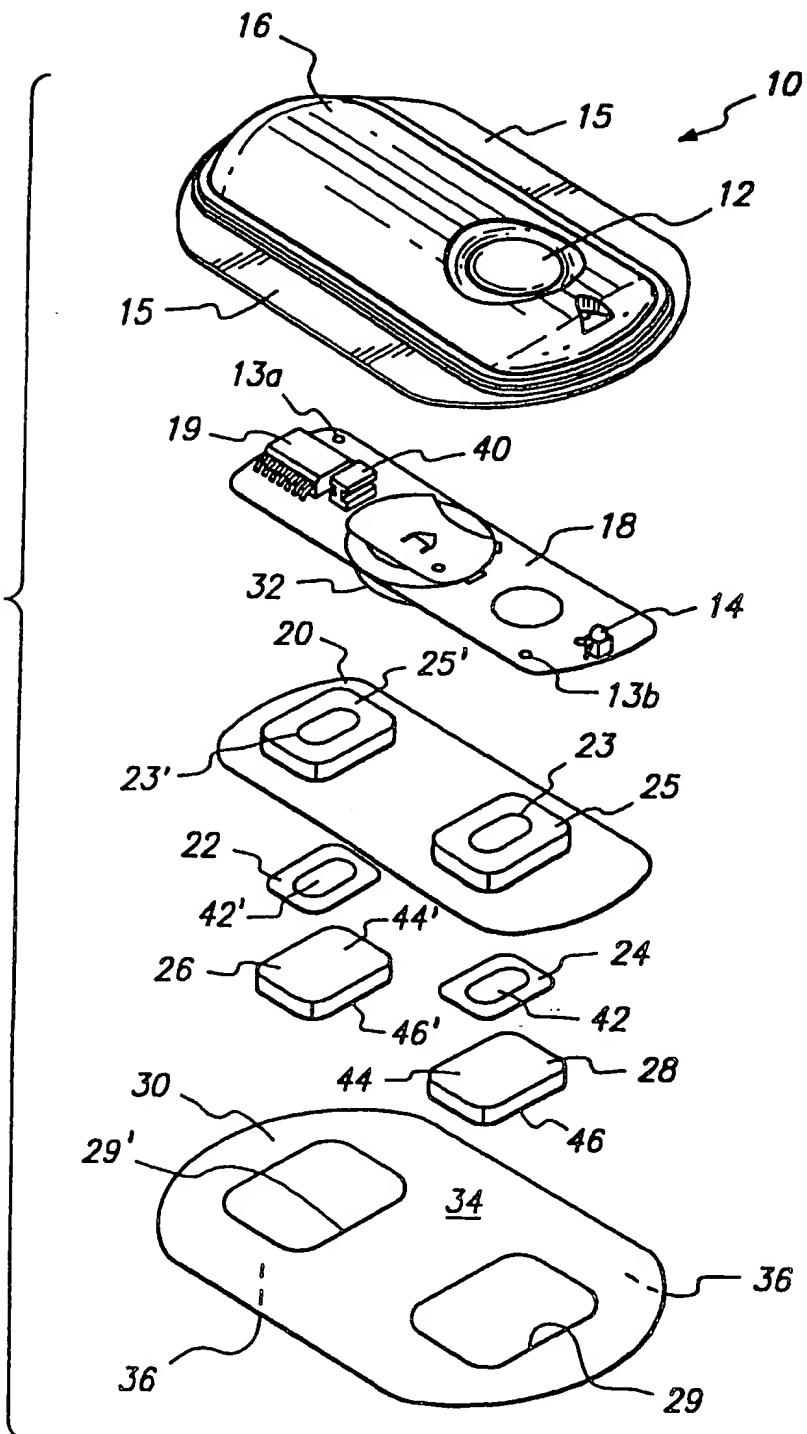
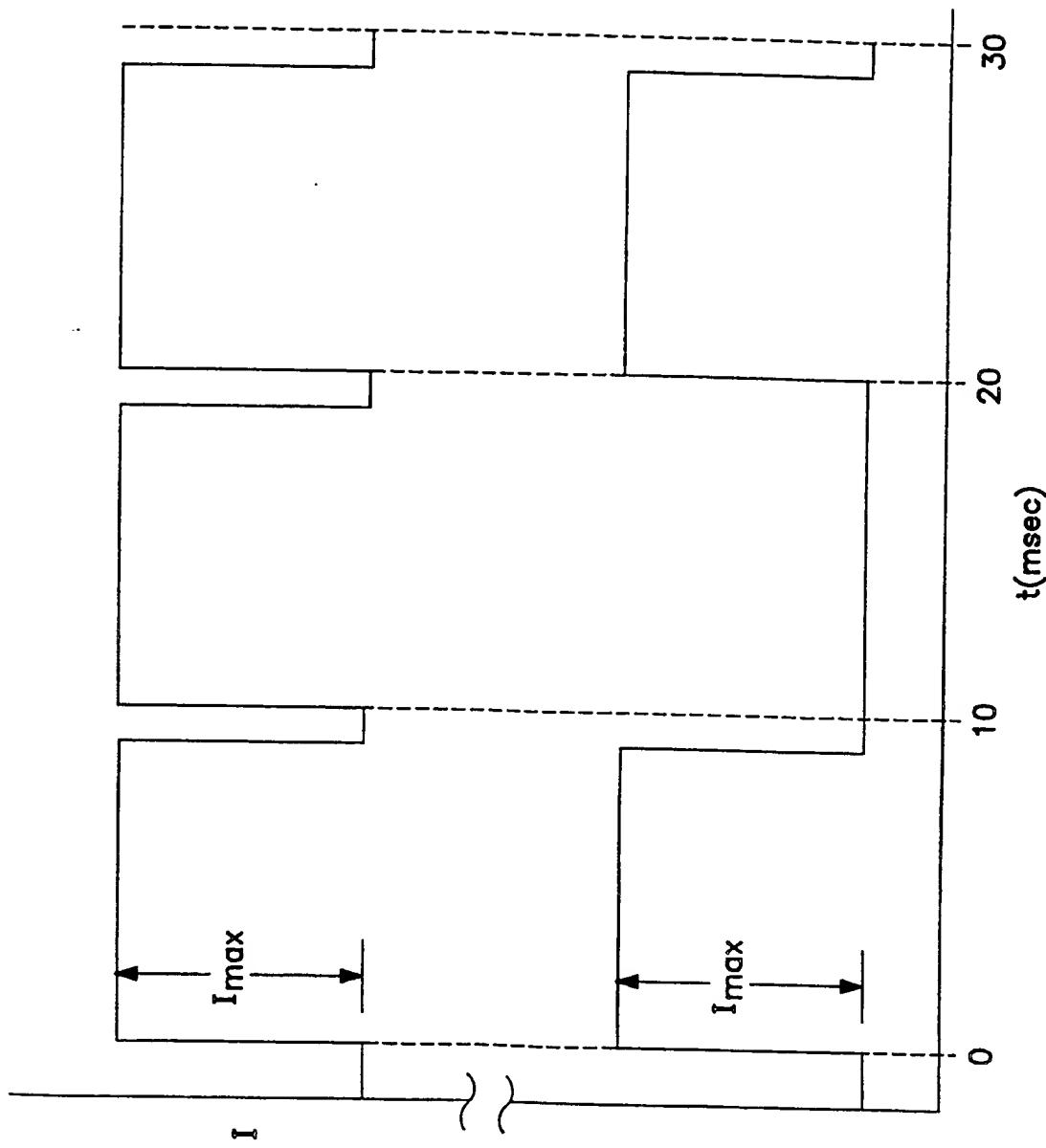
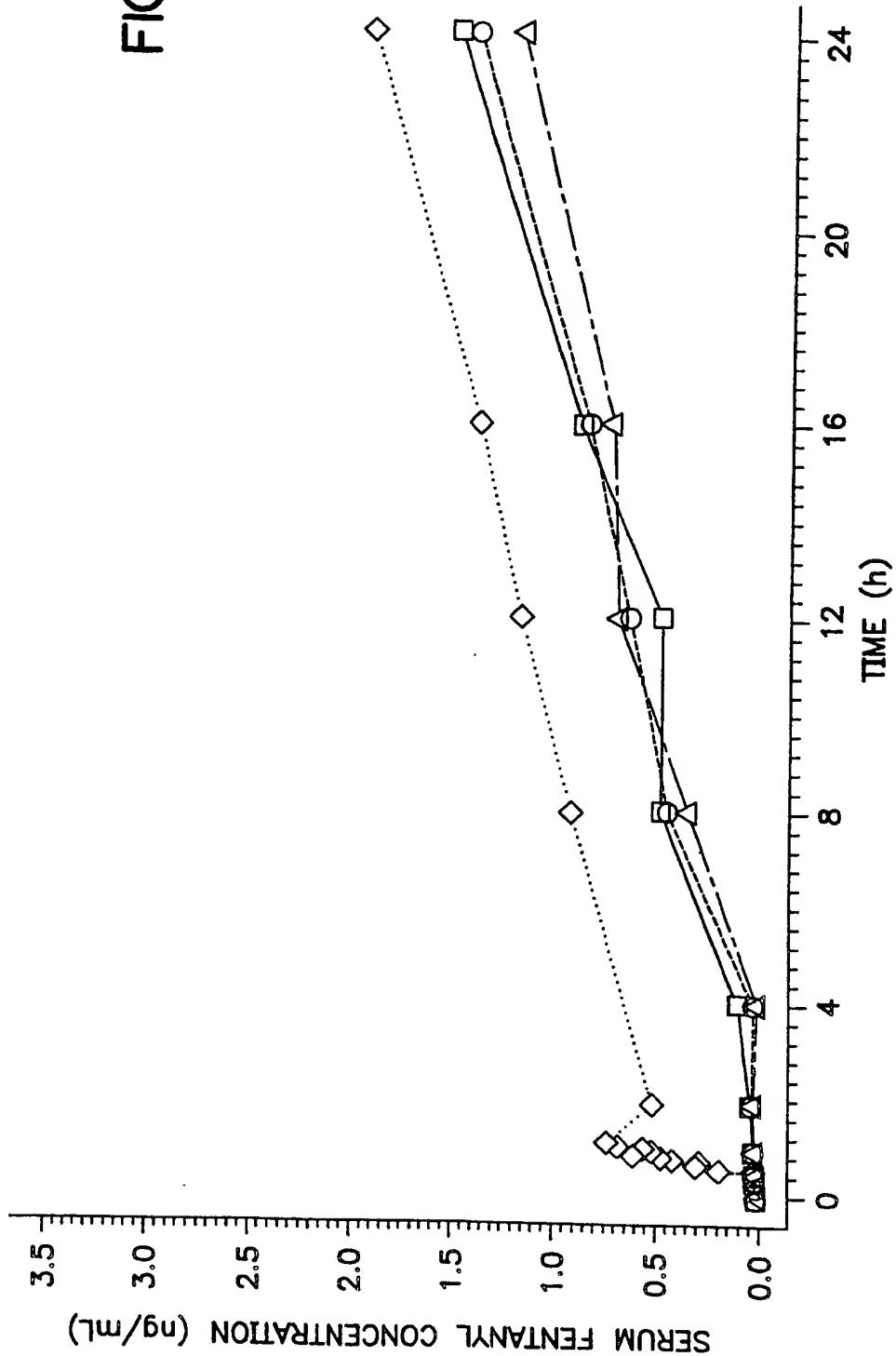


FIG. 4



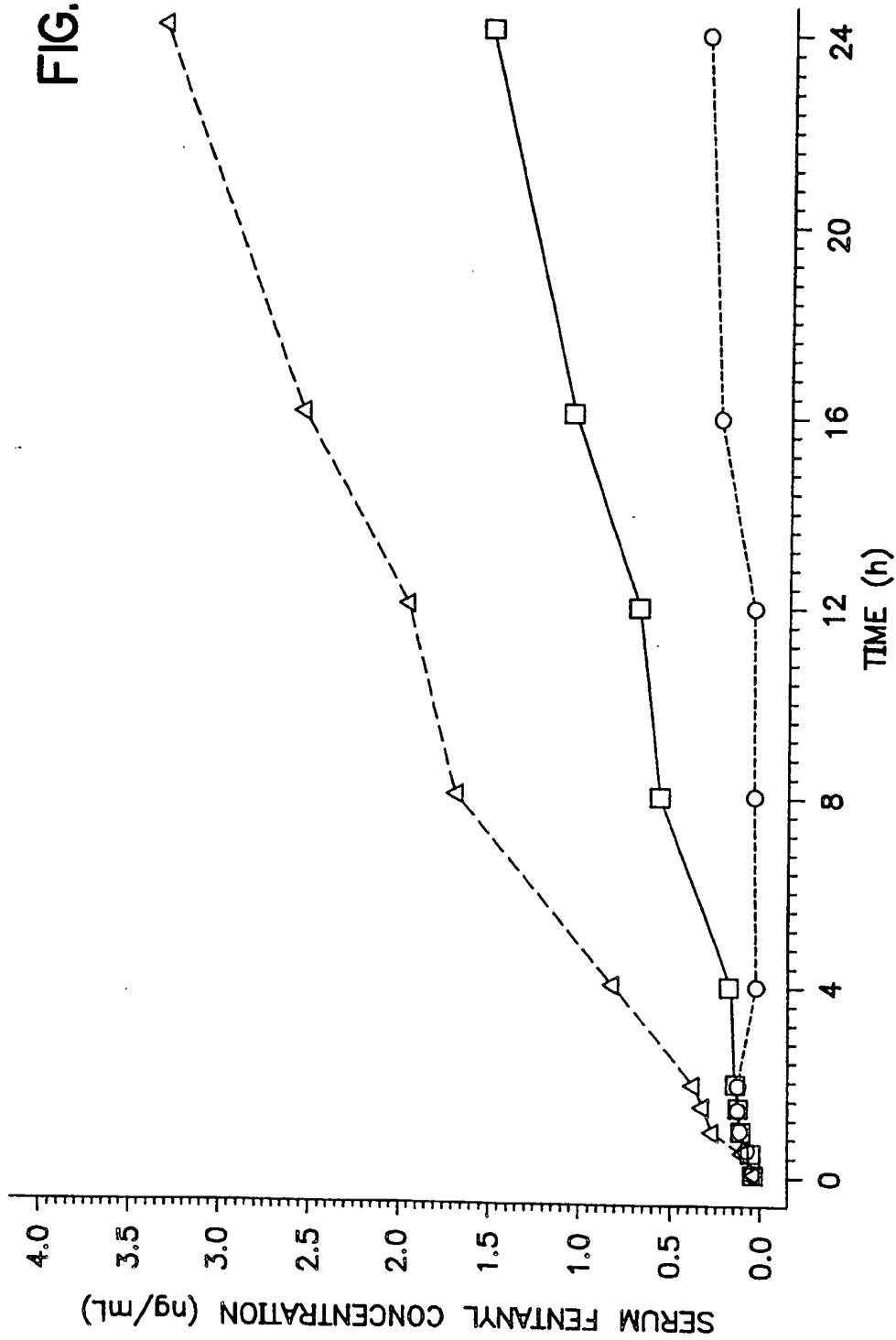
5 / 8

FIG. 5



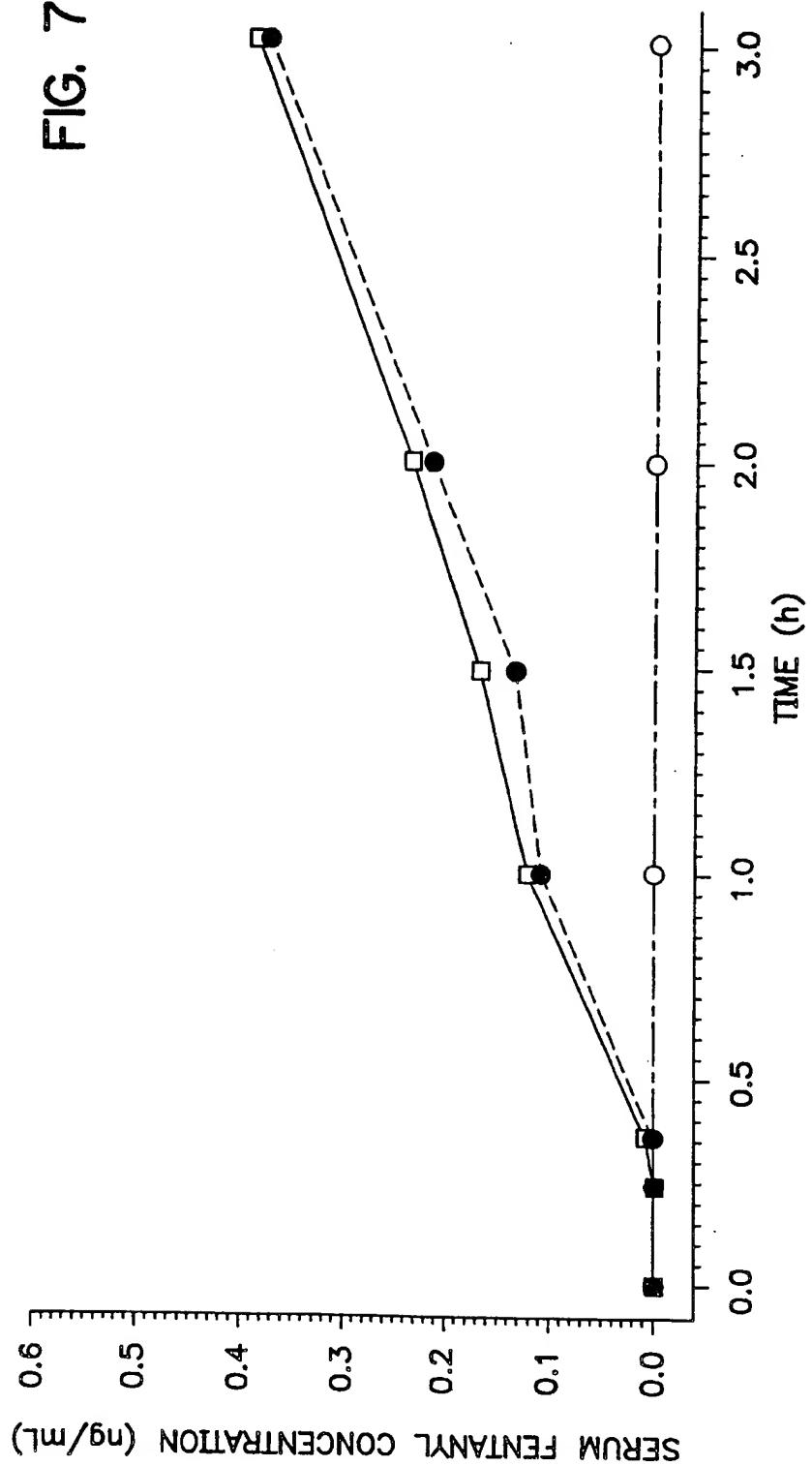
6 / 8

FIG. 6



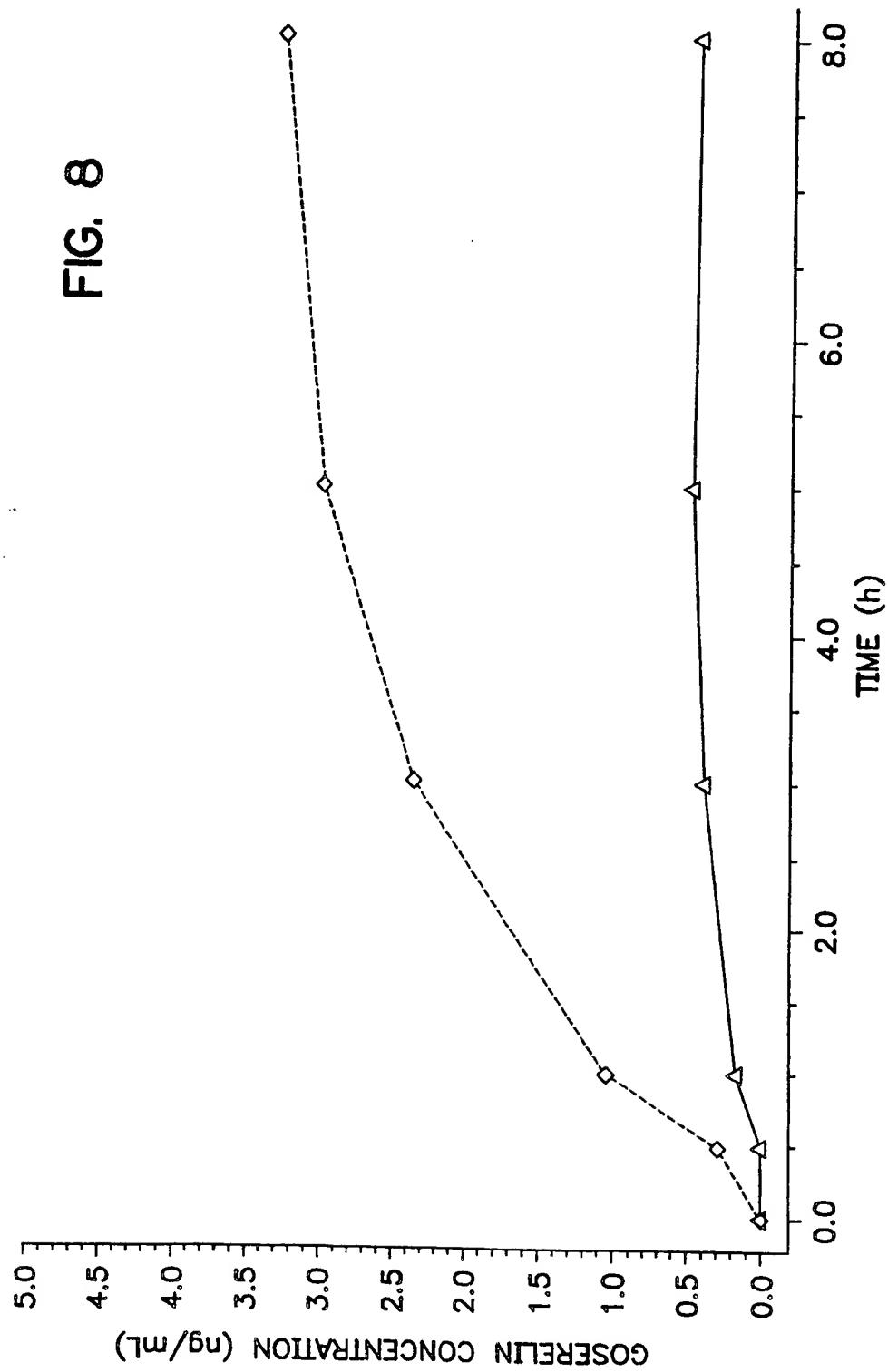
7 / 8

FIG. 7



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FIG. 8



INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/10128

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61N1/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A		

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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1

Date of the actual completion of the international search

12 November 1996

Date of mailing of the international search report

29.11.96

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INTERNATIONAL SEARCH REPORT

International Application No PCT/US 96/10128	
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